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Quantitative Structure-Activity Studies of Cyclic Phosphorothionates and Phosphates

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In order to understand the dependence of the anti-acetylcholinesterase, insecticidal activities and hydrolysis rate upon the substituents at the phosphorus atom and p-position relative to the phenyl ester group of saligenin cyclic phosphorothionates and phosphates, regression analysis was applied to the representative salithion (2-methoxy-4*H*-1, 3, 2-benzodioxaphosphorin 2-sulfide) and salioxon (2-methoxy-4*H*-1, 3, 2-benzodioxaphosphorin 2-oxide) analogs. For the insecticidal activity of salithion analogs, steric parameter was important in transport process of the compounds to the biological site of action as well as in the interaction with the site : the smaller the substituent at the phosphorus atom and the p-position, the more potent the insecticidal activity. Whereas for the insecticidal activity and hydrolysis rate of salioxon analogs, electronic nature was important : the more electronegative the phosphorus atom, the more potent the insecticidal activity and the more contributes the substituent at the phosphorus atom in resonance, the more resistant to the hydrolysis. For the anti-acetylcholinesterase activity of salioxon analogs, hydrophobic nature was important : the less hydrophobic the substituent at the phosphorus atom, the more potent the anti-acetylcholinesterase activity.

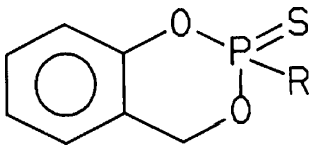
INTRODUCTION

Although many different organophosphorus compounds are important pesticides in use, few have a cyclic structure with phosphorus as a ring member. Six-membered cyclic phosphorothionate salithion has been known as an insecticide (Eto et *al., 1963).* Five-membered cyclic phosphorothionates, 4-isobutyl-2-methoxy-1, 3, 2-oxazaphospholidine 2-sulfide (Eto et al., 1981) and 2-methoxy-5-phenyl-1, 3, 2-oxazaphospholidine 2-sulfide (5-PMOS, Wu et al, 1988) were derived from L-leucine and octopamine analog 2-amino-1-phenylethanol, respectively, as potent insecticides. In order to optimize the biological activity of oxazaphospholidines, numerous structural modifications were made and quantitative structure-activity relationship (QSAR) was analyzed in 5-PMOS analogs (Hirashima et al., 1990). This paper describes the QSAR analysis of salithion and salioxon analogs in order to understand the dependence of biological activity upon the substituents.

MATERIALS AND METHODS

QSAR calculations were made by an NEC PC-9801VM personal computer system using a program for the QSAR analysis.

Table 1. Regression analysis of structure-insecticidal activity against susceptible house fly (*Musca domestica* vicina Macquart) by topical application for salithion analogs substituted at the phosphorus atom.



R	LD_{50}[a] (μg/fly)	pLD_{50}(mol/fly)			B_5[c]
		Obsd.	Calcd.[b]	Dev.	
Me	0.31	8.81	9.51	-0.70	2.04
Et	0.08	9.43	9.01	0.42	3.17
*i*Pr	0.09	9.40	9.01	0.39	3.17
Ph	0.30	8.94	9.03	− 0.09	3.11
CH_2Cl	1.14	8.31	8.88	− 0.57	3.46
OMe	0.05	9.64	9.05	0.59	3.07
OEt	0.30	8.88	8.92	− 0.04	3.36
OPh	2.00	8.14	7.81	0.33	5.89
SMe	0.18	9.11	8.97	0.14	3.26
SEt	0.90	8.44	8.65	-0.21	3.97
SPr	2.20	8.07	8.21	-0.14	4.98
SBu	10.00	7.45	7.93	-0.48	5.61
NHMe	0.04	9.69	9.05	0.64	3.08
NHEt	0.48	8.68	8.90	-0.22	3.42
NMe_2	0.38	8.81	9.05	-0.24	3.08
NEt_2	0.63	8.64	8.47	0.17	4.39

[a]Cited from the data by Eto (1965 and 1968).
[b]Calculated by Eq.(1).
[c]Cited from a brochure of Verloop (1983) provided by Prof. T. Fujita

RESULTS AND DISCUSSIONS

In order to understand quantitatively the dependence of the insecticidal activity upon the substituent at the phosphorus atom, regression analysis was applied to the representative salithion analogs listed in Table 1. The best equation obtained was

$$pLD_{50} = 4.406\ (\text{i}0.864) - 0.441\ (\pm 0.226)\ B_5 \qquad (1)$$

where $n = 16$, $s = 0.420$, $r = 0.746$, $F = 17.5$. pLD_{50} value, the log of the reciprocal of the dose (mol/fly) required to kill 50 % of the fly after 24 hr, was used as an insecticidal activity ; STERIMOL B_5, the maximum width in angstrom from the axis connecting phosphorus atom and the α atom of the substituent (Verloop, 1983) ; n, the number of data points ; r, the correlation coefficient ; s, the standard deviation ; F, the value of the F-test. The figures in the parentheses are the 95 % confidence intervals. Use of other parameters [e. g., the hydrophobic parameter π, given by $\pi = f_X - f_H$ (f_X is the

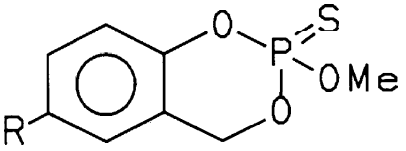
hydrophobic fragmental constant of substituent X and f_H is that of hydrogen) (Hansch and Leo, 1979 ; Hansch et *al., 1973* and 1977) or measured by Kamoshita for substituted phenyl dimethylphosphates (1980) ; the Hancock steric parameter E_s^c (Hancock, 1961 ; Unger and Hansch, 1976) ; the Taft-Kutter Hansch steric parameter E_s (Hansch and Leo, 1979 ; Kutter and Hansch, 1969) ; Swain-Lupton-Hansch field and resonance effect constants F and R (Swain and Lupton, 1968), molar refractivity MR (Hansch *et al.,* 1973 and 1977) ; STERIMOL L and B_1 (Verloop, 1983) ; electronic constant σ (Taft, 1956) ; electronic inductive and resonance constants σ_I and σ_R (Charton, 1981)] instead of B_5 or addition of the other parameters to Eq. (1) does not improve the correlation. The negative B_5 term means that the smaller the sub'stituent at the phosphorus atom, the more potent the insecticidal activity.

In order to understand the dependence of insecticidal activity upon the substituent at #-position relative to the phenyl ester group of saligenin cyclic phosphorothionate, regression analysis was applied to the representative salithion analogs listed in Table 2. The best equation obtained was

$$p\mathrm{LD}_{50} = 5.691\ (\mathrm{k}1.867)\ \$0.255\ (\mathrm{i}0.247)\ \pi^2 - 2.225\ (\pm 1.249)\ B_1 \qquad (2)$$

where n = 7, $s = 0.279$, $r = 0.930$, $F = 12.8$, although it is significant at a level of 98.1 % as examined by the F-test. B_1 is the minimum width in angstrom from the axis connecting benzene ring at the \$-position and α atom of the substituent (Verloop, 1983), and significant at a level of 95.4 % by a t-test. Eqs. (1), (4) -(6) are significant at a

Table 2. Regression analysis of structure-insecticidal activity against susceptible house fly (*Musca domestica* vicina Macquart) by topical application for salithion analogs substituted at the p-position.



R	LD_{50}[a] (μg/fly)	$p\mathrm{LD}_{50}$(mol/fly)			B_1[c]	π^2[d]
		Obsd.	Calcd.[b]	Dev.		
H	0.05	9.64	9.47	0.17	1.00	0
Me	2.00	8.06	8.39	-0.33	1.52	0.314
Ph	0.40	8.86	8.87	-0.01	1.71	3.842
OMe	0.55	8.67	8.69	-0.02	1.35	0
Cl	1.75	8.18	7.82	0.36	1.80	0.504
Ac	2.50	8.01	8.21	-0.20	1.60	0.308
NO_2	3.00	7.94	7.93	0.01	1.70	0.078

[a]Cited from the data by Eto *et al.*(1968).
[b]Calculated by Eq. (2).
[c]Cited from a brochure of Verloop (1983) provided by Prof. T. Fujita
[d]Calculated from the data by Hansch and Leo (1979).

level of 99 % and all terms in Eqs. (1) - (6) are justified more than 99 % unless otherwise noted. Use of other parameters (e. g., π, E_s^c, E_s. **F, R, MR**, **L**, B_5, σ, σ_I and σ_R) instead of B_1 and π^2 or addition of the other parameters to Eq. ('2) does not improve the correlation. According to Eq. (2), steric nature is important and the negative B_1 term means that the smaller the substituent at the @-position, the more potent the insecticidal activity.

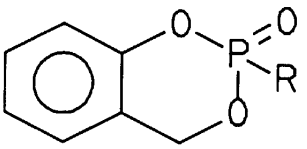
In order to understand the dependence of the insecticidal activity upon the substituent at the phosphorus atom, regression analysis was applied to the representative salioxon analogs listed in Table 3. The best equation obtained was

$$p\mathrm{LD}_{50} = 3.926\ (\pm 0.867) + 1.384\ (\pm 1.593)\ \sigma + 0.510\ (\pm 0.459)\ E_s \qquad (3)$$

where $n = 8, s = 0.300$, $r = 0.797$, $F = 4.3$, although it is significant only at a level of 91. 9 %. σ and E_s terms are justified only at levels of 92.4 and 96.4 %, respectively. Use of other parameters (e. g., π, E_s^c, **F, R, MR**, **L**, B_1, B_5, σ_I and σ_R) instead of σ and E_s or addition of the other parameters to Eq. (3) does not improve the correlation. According to Eq. (3), the electronic nature was important : the positive σ term indicates that the more electronegative the phosphorus atom, the more potent the insecticidal activity.

In order to understand the dependence of hydrolysis upon the substituent at the phosphorus atom, regression analysis was applied to the representative salioxon

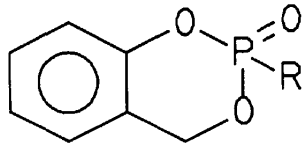
Table 3. Regression analysis of structure-insecticidal activity against susceptible house fly (*Musca domestica* vicina Macquart) by topical application for salioxon analogs substituted at the phosphorus atom.



R	LD_{50}[a] (μg/fly)	$p\mathrm{LD}_{50}$ (mol/fly)			σ[c]	E_s[cd]
		Obsd.	Calcd.[b]	Dev.		
Me	0.13	8.99	9.06	-0.07	-0.17	− 1.24
Et	0.17	9.07	9.05	0.02	-0.15	− 1.31
*i*Pr	0.33	8.81	8.85	-0.04	-0.15	− 1.71
CHCH,	0.68	8.46	8.42	0.04	-0.04	− 2.84
OMe	0.04	9.76	9.26	0.50	-0.28	− 0.55
OEt	0.33	8.81	9.24	-0.43	-0.29	− 0.55
SMe	0.09	9.39	9.40	-0.02	0.01	-1.07
NMe_2	0.30	8.63	8.63	0	-0.71	-0.61

"Cited from the data by Eto (1965 and 1968).
*Calculated by Eq. (3).
"Summation of σ_I and σ_R cited from the data by Charton (1981).
[d]Cited from the data by Unger and Hansch (1976).

Table 4. Regression analysis of structure-hydrolysis rate in M/15 phosphate buffer (pH 7.7) at 25°C for salioxon analogs substituted at the phosphorus atom.



R	K_{hyd}[a] (min^{-1}) $\times 10^{-3}$	pK_{hyd} (min^{-1})			π[c]	π^2	F[c]	R[c]
		Obsd.	Calcd.[b]	Dev.				
Me	22.2	1.65	2.05	-0.40	0.56	0.314	-0.04	-0.13
Et	4.25	2.37	2.08	0.29	1.02	1.040	1.02	-0.10
CH_2Cl	200	0.699	0.607	0.092	0.17	0.029	0.10	0.03
CHCH,	13.90	1.86	1.75	0.11	0.82	0.672	0.07	-0.08
Ph	12.80	0.893	1.142	− 0.249	1.96	3.842	0.08	-0.08
OMe	1.42	2.85	2.89	-0.04	− 0.02	0	0.26	-0.51
OEt	0.50	3.30	3.10	0.20	0.38	0.144	0.22	-0.44
OPr	0.379	3.42	3.47	-0.05	1.05	1.103	0.22	-0.45
OBu	0.329	3.48	3.75	-0.27	1.55	2.403	0.25	-0.55
OPh	6.30	2.20	1.96	0.24	2.08	4.326	0.34	-0.35
SMe	15.00[d]	1.82	1.96	-0.14	0.61	0.372	0.20	-0.18
NHMe	0.154	3.81	3.81	0	-0.47	0.221	-0.11	-0.74
NHPh	0.24	3.62	3.40	0.22	1.37	1.877	-0.02	-0.38

[a]Cited from the data by Eto (1965).
[b]Calculated by Eq. (5).
[c]Cited from the data by Hansch and Leo (1979).
[d]Cited from the data by Eto (1983).

analogs listed in Table 4. The best equation obtained was

$$pK_{hyd} = 1.239\ (\pm 0.522) - 4.005\ (\pm 1.384)\ \boldsymbol{R} \tag{4}$$

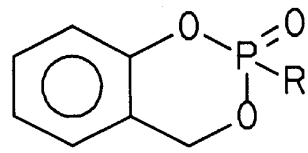
where $n = 13, s = 0.503, r = 0.887, F = 40.6$. pK_{hyd} value, the log of the reciprocal of the hydrolysis constant K_{hyd} (min^{-1}) measured in M/15 phosphate buffer (pH 7.7) at 25°C, was used as a hydrolysis index. Addition of the parameters π, π^2 and $\boldsymbol{F}$ to Eq. (4) improved the correlation to give Eq. (5)

$$pK_{hyd} = 0.680\ (\pm 0.448) + 1.538\ (\pm 0.670)\pi - 0.740\ (\pm 0.332)\ \pi^2 - 1.565(\pm 1.376)\boldsymbol{F} - 5.194\ (\pm 0.922)\boldsymbol{R} \tag{5}$$

where n = 13, s = 0.267, r = 0.978, $\boldsymbol{F = 43.9}$ and $\boldsymbol{F}$ term is significant at a level of 96.9 %. According to Eqs. (4) and (5), the resonance effect of the substituent is important to the hydrolysis of salioxon analogs. The negative $\boldsymbol{R}$ term means that the more contributes the substituent at the phosphorus atom in resonance, the more resistant to the hydrolysis.

In order to understand quantitatively the dependence of anti-acetylcholinesterase activity upon the substituent at the phosphorus atom, regression analysis was applied

Table 5. Regression analysis of structure-anti-acetylcholinesterase activity in vitro against susceptible Takatsuki strain house fly for salioxon analogs substituted at the phosphorus atom.



R	pI_{50} (M)			π^c
	Obsd.[a]	Calcd.[b]	Dev.	
Ph	6.05	5.98	0.07	1.96
MeO	7.12	7.09	0.03	-0.02
EtO	6.89	6.87	0.02	0.38
PrO	6.29	6.49	-0.20	1.05
BuO	6.42	6.21	0.21	1.55
PhO	5.80	5.92	-0.12	2.08

[a]Cited from the data by Eto *et al.* (1963).
[b]Calculated by Eq. (6).
[c]Cited from the data by Hansch and Leo (1979).

to the representative salioxon analogs listed in Table 5. The best equation obtained was

$$pI_{50} = 7.051\ (\mathbf{k0.293})\ \mathbf{-0.498}\ (\pm 0.209)\ \pi \qquad (6)$$

where $n = 6, s = 0.144, r = 0.957, F = 43.7$. pI_{50} value, the log of the reciprocal of the concentration needed for 50 % acetylcholinesterase inhibition (M), was used as an anti-acetylcholinesterase activity. Use of other parameters (e. g., π^2, E_s^c, E_s, F, R, MR, L, B_1, B_5, σ, σ_I and σ_R) instead of π or addition of the other parameters to Eq. (6) does not improve the correlation. The negative π term means that the less hydrophobic the substituent at the phosphorus atom, the more potent the anti-acetylcholinesterase activity.

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